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A Study on the Relationship of Vitamin A and E Levels in Umbilical Cord Blood with Respiratory Distress Syndrome in Preterm Infants

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【**Abstract**】 **Background** Respiratory distress syndrome（RDS）is an important cause of death in preterm infants, which needs to be constantly strengthened in clinical prevention and treatment, but the relationship of umbilical cord blood vitamin A and E levels with the development of RDS in preterm infants has been rarely reported. **Objective** To investigate the relationship of vitamin A and E levels in umbilical cord blood with RDS in preterm infants. **Methods** A total of 304 preterm infants in the Fourth Hospital of Shijiazhuang from January 2021 to January 2022 were selected and divided into the RDS group（*n*=120）and non-RDS group（*n*=184）according to the incidence of RDS. Clinical features that may be related to the occurrence of RDS in preterm infants were collected, vitamin A and E levels in umbilical cord blood were detected. Multivariate Logistic regression analysis was used to analyze the influencing factors of the occurrence and severity of RDS in preterm infants. **Results** The gestational age, birth weight, vitamin A and E levels in umbilical cord blood of preterm infants in the RDS group were lower than those in the non-RDS group, the proportions of newborn's Apgar score in one-minute ≤ 7, newborn's Apgar score in five-minute ≤ 7, and incidence of vitamin A deficiency were higher in the RDS group than those in the non-RDS group（*P*<0.05）. There were 86 cases with mild RDS and 34 cases with severe RDS in the RDS group；the vitamin A level in umbilical cord blood in cases with severe RDS was significantly lower than cases with mild RDS, while the incidence of vitamin A deficiency was significantly higher than cases with mild RDS（*P*<0.05）. Multivariate Logistic regression analysis showed that vitamin A level in umbilical cord blood was the influencing factor of the occurrence of RDS in preterm infants〔*OR*=2.208, 95%*CI*（1.156, 4.218）, *P*<0.05〕, and vitamin A deficiency was the influencing factor of the occurrence of severe RDS〔*OR*=6.835, 95%*CI* （2.537, 18.416）, *P*<0.05〕. **Conclusion** Vitamin A and E levels in umbilical cord blood are relatively lower in preterm infants with RDS, vitamin A level is the influencing factor of the occurrence and severity of RDS in preterm infants, suggesting that vitamin A supplementation should be applied during pregnancy to reduce the occurrence or severity of RDS in preterm infants.

【Key words】 Respiratory distress syndrome, newborn；Infant, premature；Fetal blood；Vitamin A；Vitamin E；Risk factors

Neonatal respiratory distress syndrome （RDS） is the main clinical manifestation of respiratory distress that occurs shortly after birth. Neonatal respiratory distress syndrome （RDS） is characterized by progressive respiratory distress and subsequent hypoxia and acidosis occurring shortly after birth. The main clinical manifestations of RDS are progressive respiratory distress shortly after birth, followed by hypoxia, acidosis and, in severe cases, respiratory failure. RDS is most common in preterm infants and is a major cause of bronchopulmonary dysplasia and other serious complications in newborns. RDS is most common in preterm infants and is an important cause of serious neonatal complications such as bronchopulmonary dysplasia and death in preterm infants. Pulmonary surfactant （PS） deficiency is the main cause of RDS. The lack of pulmonary surfactant （PS） is the main cause of RDS. Since the alveoli appear in the fetus at 25 weeks of gestational age, the lungs continue to develop. After that, the lungs continue to develop and the number of alveoli increases until the number of alveoli is almost the same at 36 weeks of gestation. After that, the number of alveoli continued to increase until the number of alveoli stabilized at 36 weeks of gestational age, and the type II epithelial cells in the alveoli began to secrete PS. After that, the number of alveoli continued to develop and the number of alveoli increased until the number of alveoli stabilized at 36 weeks of gestational age, when type II epithelial cells in the alveoli began to secrete PS. Therefore, the younger the gestational age, the higher the incidence of RDS in newborns. A study showed that the incidence of RDS in neonates with gestational age of 35 weeks was 4.6%, while the incidence of RDS in neonates with gestational age of 36 weeks was 4.6%. The incidence of RDS in neonates at 35 weeks of gestational age was shown to be 4.6%, whereas in neonates at 36 weeks of gestational age the incidence of RDS decreased to 1.6%[1].

Vitamin A and vitamin E are fat-soluble vitamins and essential vitamins. FERNANDES-SILVA et al.[2] showed that retinoic acid, the main active form of vitamin A, participates in its regulation playing an important role in lung development and alveolar formation, and vitamin A deficiency is associated with a variety of lung diseases[3]. KOLLECK et al[4] showed that vitamin E is involved in alveolar type II epithelium and is an indispensable component of PS synthesis and is secreted together with PS into the interalveolar space. Currently, clinical studies on the relationship between vitamins and neonatal RDS have mainly focused on the relationship between serum vitamin A levels and neonatal RDS, and have not been fully clarified, while the relationship between vitamin E and neonatal RDS has been less frequently reported. Since neonatal RDS mostly occurs within 6 h after birth, we chose to collect

umbilical cord blood from preterm infants at birth to measure the levels of vitamin A and E, in order to avoid the influence of postnatal diseases or clinical treatment. In this study, we investigated the relationship between umbilical cord blood vitamin A and E levels and RDS in preterm infants, in order to provide a reference for the clinical prevention and treatment of RDS in preterm infants.

1 Objects and Methods

1.1 Research Subjects 304 preterm infants born in Shijiazhuang No. 4 Hospital from January 2021 to January 2022 were selected and divided into 120 cases in the RDS group and 184 cases in the non-RDS group according to the occurrence of RDS. Inclusion criteria: （1）gestational age <36 weeks; （2）cord blood collection from the fetal end was completed immediately after umbilical cord disconnection; （3）guardians of preterm infants were informed of the purpose of the cord blood examination, and the guardians of the preterm infants gave their informed consent to the study and signed an informed consent form; （4）the pregnancy examination of the mothers of the preterm infants did not reveal the presence of congenital diseases in the fetuses such as complex congenital heart disease and chromosomal disorders, and so on. Exclusion criteria: （1）congenital diseases, such as congenital diaphragmatic hernia, metabolic diseases, etc., were found after birth; （2）pulmonary hemorrhage, pneumothorax, coeliac chest, etc., appeared immediately after birth; （3）mothers of preterm infants suffered from chronic liver and kidney diseases. This study was approved by the Ethics Committee of the Fourth Hospital of Shijiazhuang City （approval number: 20230089）.

1.2 Diagnostic and grading criteria of RDS in preterm infants Refer to the diagnostic criteria of neonatal RDS in Practical Neonatology （5th edition）[5]: （1） Clinical manifestations: progressive dyspnea and severe hypoxic respiratory failure appeared immediately after birth; （2） Chest X-ray findings: the distribution of the lesions in the lungs was relatively uniform, and the early stage was characterized by a decrease in the translucency of the lungs, which showed a "hairy-glass" change, and in severe cases, the entire lung field showed a "white lung" change. （2） Chest X-ray findings: the lesions of both lungs are distributed evenly, the translucency of both lungs is reduced in the early stage, showing "hairy glass-like" changes, and in severe cases, the whole lung field shows "white lung", and the bronchial insufflation sign is visible. Grading criteria of RDS in preterm infants: Grade I with decreased lung translucency, tiny granular reticular shadows in the lung field, and clear cardiac shadows; Grade II with further aggravation of the severity of the lesion on the basis of Grade I, with obvious bronchial inflation and extension to the middle of the lungs in the direction of adduction; and Grade II with continued aggravation of the severity of the lesion on the basis of Grade II, with bronchial inflation and increased lung size and increased lung size. On the basis of

grade II, the severity of the lesion continues to aggravate, the bronchial inflation sign is obvious, the cardiac shadow and diaphragmatic shadow become poorly defined, and the whole lung field shows "hairy glass-like" changes as grade III; the severity of the lesion is very serious, the bronchial dilatation sign is very obvious, and the whole lung field shows a "white lung"-like pattern, but the thorax and diaphragm are free of lesions as grade IV. Grade IV was defined as severe lesions with obvious signs of bronchiectasis and "white lung" in the whole lung field but no lesions in the thorax and diaphragm. In this study, RDS grades I to II were defined as mild cases, and RDS grades III to IV were defined as severe cases.

1.3 Treatment All preterm infants were treated within 12 hours after birth, among which nutritional support and symptomatic treatment were given to preterm infants in the non-RDS group, while preterm infants in the RDS group were assisted with respiration on a ventilator of appropriate mode according to respiratory conditions on the basis of nutritional support and symptomatic treatment. For high-risk preterm infants who breathe spontaneously after birth but may develop RDS （e.g., <30 weeks of gestational age, but do not require mechanical ventilation with tracheal intubation）, or if oxygen is administered by nasal cannula, mask, or hood but the inspired oxygen concentration （FiO_2） is >0.3, the partial pressure of arterial oxygen is <50 mmHg （1 mmHg=0.133 kPa）, or the transcutaneous oxygen saturation level （$TcSO_2$） is <90%, then give them continuous positive pressure ventilation, and make sure that the positive pressure at end of expiration is at least 6 cmH_2O （1 cmH_2O=0.098 kPa）, oxygen flow rate of 6~8 L/min, and FiO2 adjusted according to TcSO2; for preterm infants without spontaneous respiration after birth, non-invasive ventilator was used for assisted respiration with FiO2>0.6, arterial partial pressure of oxygen <60 mmHg, or TcSO2<85%, and arterial partial pressure of carbon dioxide >60 mmHg with persistent acidosis （pH<90%）. When acidosis （pH <7.2） was present, the ventilator was switched to invasive ventilator assisted breathing, and the synchronized intermittent command ventilation mode was selected, with the following initial parameter settings: peak inspiratory pressure of 20-25 cmH_2O, positive end-expiratory pressure of 4-6 cmH_2O, respiratory rate of 30-40 breaths/min, inspiratory time of 0.3-0.4 s, and tidal volume of 4-6 mL/kg. When FiO2≥0.3 under invasive ventilator-assisted respiration or non-invasive ventilator-assisted respiration, 40~100 mg/kg of bovine lung surfactant （manufacturer: China Resources Shuanghe Pharmaceutical Co., Ltd., batch no.: 2011994） was added for alternative treatment, which was administered intratracheally.

1.4 Observation indexes A special person is responsible for collecting clinical characteristics that may be related to the occurrence of RDS in preterm infants, mainly including the mother's condition and preterm infant's condition, of which the mother's condition involves age, mode of delivery, prenatal application of hormones, preterm rupture of

membranes >18 h, and the occurrence of gestational diabetes mellitus, gestational hypertension, chorionic villus amnionitis, etc. The conditions of preterm infants involved gestational age, birth weight, sex, 1 min Apgar score≤7, 5 min Apgar score ≤ 7 （according to the diagnostic criteria of neonatal asphyxia[5-6], 1 min Apgar score≤7, 5 min Apgar score ≤ 7 are the necessary conditions for the diagnosis of neonatal asphyxia）, and the levels of vitamins A and E in the umbilical cord blood as well as the conditions of vitamins A and E deficiency. The diagnostic criteria for vitamin A and E deficiency are as follows: referring to the criteria promulgated by the WHO in 2011 and previous studies [7-8], in the present study, cord blood vitamin A level <100.0 μg/L was regarded as vitamin A deficiency, cord blood vitamin A level <100.0 μg/L was regarded as vitamin A deficiency and <200.0 μg/L was regarded as subclinical vitamin A deficiency.

1.5 Umbilical cord blood vitamin A and E level detection method 3 mL of umbilical cord blood was extracted from the fetal end of the umbilical cord of preterm infants after umbilical cord disconnection and placed in test tubes without anticoagulation treatment, and then stood at 0~4℃, protected from light, and centrifuged for 15 min （with a centrifugal radius of 10 cm） in order to isolate the serum, and then after the removal of proteins and impurities, extraction of the active ingredients by n-hexane, and re-solubilization in methanol, the blood was analyzed by using Agilent UPLC1290 liquid-phase liquid-phase analysis. Agilent UPLC1290 liquid chromatography, high performance liquid chromatography to detect the level of vitamin A and E in umbilical cord blood and produce data curves, the error calibration is not allowed to exceed 15%, and finally through the Westgard multi-specification quality control method to determine whether the test results are qualified or not.

1.6 Statistical methods The data were statistically analyzed using Excel and SPSS 25.0 software. Measurement data conforming to normal distribution were expressed as（$\bar{x}\pm s$）, and two independent samples t-test was used for comparison between two groups; measurement data not conforming to normal distribution were expressed as M（P_{25}, P_{75}）, and Mann-Whitney U test was used for comparison between two groups. Count data were expressed as relative numbers, and comparisons between two groups were made using the χ^2 test. The χ^2 test or Fisher's exact probability method was used to compare the two groups. Multifactorial Logistic regression analysis was used to analyze the factors affecting the occurrence of RDS and the severity of RDS in preterm infants. A difference of P<0.05 was considered statistically significant.

2 Results

2.1 Comparison of clinical characteristics of preterm infants in the two groups The differences between the two groups in terms of age of mothers, mode of delivery, proportion of prenatal hormones, proportion of preterm

premature rupture of membranes >18 h, and the incidence rates of gestational diabetes mellitus, gestational hypertension, and chorioamnionitis were statistically insignificant （P>0.05）, as shown in table 1.

Table 1 Comparison of clinical characteristics of mothers of preterm infants in the two groups

Group	Number of cases	Mother's age〔M（P_{25}, P_{75}）, year〕	Mode of delivery [cases （%）]		Prenatal hormone use[cases （%）]	Premature rupture of membranes >18 h[cases （%）]	Gestational diabetes mellitus[cases （%）]	Hypertension during pregnancy[cases （%）]	Chorionic villus amnionitis [cases （%）]
			normal delivery	cesarean section					
Non-RDS Group	184	29（26, 31）	145（78.8）	39（21.2）	112（60.9）	62（33.7）	33（17.9）	42（22.8）	14（7.6）
RDS Group	120	30（27, 32）	89（74.2）	31（25.8）	82（68.3）	43（35.8）	20（16.7）	32（26.7）	16（13.3）
χ^2（Z）value		-1.704[a]	0.881		1.752	0.147	0.081	0.582	2.676
P value		0.088	0.348		0.186	0.702	0.776	0.446	0.102

Note：RDS=respiratory distress syndrome；[a] indicates Z value

In the RDS group, the gestational age and body mass of preterm infants were smaller than those in the non-RDS group, the proportion of infants with 1-min Apgar score ≤7, the proportion of infants with 5-min Apgar score ≤7 were higher than those in the non-RDS group, and the levels of vitamin A and E in umbilical cord blood were lower than those in the non-RDS group, and the differences were statistically significant （P<0.05）; the differences in the genders of preterm infants in the two groups were statistically meaningless （P>0.05）, as shown in table 2.

Table 2 Comparison of clinical characteristics of preterm infants in the two groups

Group	Number of cases	Gestational age〔M（P_{25}, P_{75}）, week〕	Gender[cases （%）]		Birth weight[cases （%）]	Apgar score[cases （%）]		Vitamin A（$\bar{x}\pm s$, μg/L）	Vitamin E（$\bar{x}\pm s$, mg/L）
			Male	Female		1 min score ≤7	5 min score ≤7		
Non-RDS	184	34.5（33.0, 35.0）	95（51.6）	89（48.4）	2.3±0.4	28（15.2）	9（4.9）	156.5±48.9	3.79±1.02

Group									
RDS Group	120	32.5（30.0, 34.2）	68（56.7）	52（43.3）	1.8±0.6	35（29.2）	19（15.8）	139.0±42.5	3.55±0.97
Test statistic value		-7.436[a]	0.741		7.129[b]	8.602[b]	10.399	3.204	2.070
P value		<0.001	0.389		<0.001	0.003	0.001	0.002	0.039

Note：[a] indicates *Z* value，[b] indicates chi-square value, the remaining test statistic values were *t* values

2.2 Comparison of vitamin A and E deficiencies in preterm infants in the two groups The incidence of vitamin A deficiency in preterm infants in the RDS group was 25.0% （30/120）, which was higher than that in the non-RDS group （13.0%）, with a statistically significant difference （χ^2=7.108, *P*=0.008）; the incidence of subclinical vitamin A deficiency in preterm infants in the RDS group was 70.8% （85/120）, while that in the non-RDS group was 85/120, with a statistically significant difference（*P*<0.05）. The incidence of subclinical vitamin A deficiency in preterm infants was 70.8% （85/120） in the RDS group and 69.6% （128/184） in the non-RDS group, and the difference between the two groups was not statistically significant（χ^2=0.056, *P*=0.813）; the incidence of vitamin E deficiency in preterm infants was 92.5% （111/120） in the RDS group and 91.3% （168/184） in the non-RDS group, and the difference between the two groups was not statistically significant（χ^2=0.138, *P*=0.004）.

2.3 Multifactorial Logistic regression analysis of factors affecting the development of RDS in preterm infants The development of RDS in preterm infants was taken as the dependent variable （assigned value: yes =1, no=0）, and the observational indexes that had statistically significant differences in the univariate analysis were taken as the independent variables [gestational age （assigned value: measured value）, birth weight （assigned value: measured value）, 1-min Apgar score ≤7（assigned value: yes =1, no =0）, gestational age ≤1 （assigned value: yes =1, no =0）, and 1-min Apgar score ≤1（assigned value: yes =1, no =0）]. （Assignment: yes =1, no =0）, 5 min Apgar score ≤ 7 （Assignment: Yes = 1, No = 0）, cord blood vitamin A level （Assignment: measured value）, cord blood vitamin E level （Assignment: measured value）] were subjected to multifactorial logistic regression analysis, and the results showed that the gestational age, body mass at birth, and cord blood vitamin A level were the influencing factors for the occurrence of RDS in preterm infants（*P*<0.05）, as shown in table 3; and the corrections of gestational age, body mass at birth, and cord blood vitamin A level were also found to be the influencing factors for the occurrence of RDS in preterm infants （*P*<0.05）. After correcting for gestational age and body mass, it was found that cord blood vitamin A level was still an influential factor in the occurrence of RDS in preterm infants [*OR*=2.208,

95% *CI* （1.156, 4.218）, *P*<0.05].

Table 3 Multivariate Logistic regression analysis of influencing factors of RDS in preterm infants

Variable	*B*	*SE*	Wald χ^2值	*P* value	*OR*（95%*CI*）
Gestational age	-0.231	0.114	4.106	0.043	0.794（0.635, 0.992）
Birth weight	-1.126	0.475	5.611	0.018	0.324（0.128, 0.823）
1 min Apgar score≤7分	0.450	0.425	1.124	0.299	1.569（0.682, 3.605）
5 min Apgar score≤7分	0.674	0.623	1.171	0.279	1.962（0.579, 6.652）
Vitamin A	-0.095	0.030	9.785	0.002	0.909（0.856, 0.965）
Vitamin E	-0.222	0.141	2.470	0.801	0.801（0.607, 1.056）

2.4 Comparison of cord blood vitamin A and E levels and vitamin A and E deficiencies in preterm infants with different degrees of severity of RDS In the RDS group, 86 preterm infants were mildly ill and 34 were severely ill. The cord blood vitamin A level of preterm infants with severe RDS was lower than that of preterm infants with mild RDS, and the incidence of vitamin A deficiency was higher than that of preterm infants with mild RDS, and the difference was statistically significant（*P*<0.05）; there were no statistically significant differences in the cord blood vitamin E level, the incidence of subclinical deficiency of vitamin A, and vitamin E deficiency of preterm infants with different degrees of severity of RDS（*P*>0.05）, as shown in table 4. The differences were not statistically significant （*P*>0.05）, see table 4.

Table 4 Comparison of vitamin A and E levels and deficiency rates of preterm infants with different severity of RDS

RDS severity	Number of cases	Vitamin A（$\bar{x}\pm s$, μg/L）	Vitamin E（$\bar{x}\pm s$, μg/L）	Vitamin A deficiency[cases （%）]	Vitamin A subclinical deficiency[cases （%）]	Vitamin E deficiency [cases （%）]
Mild	86	144.4±42.2	3.60±1.01	16（18.6）	63（73.3）	78（90.7）
Severe	34	125.3±40.8	3.40±0.84	14（41.2）	22（64.7）	33（97.1）
χ^2（*t*）值		7.271[a]	2.631[a]	6.621	0.862	—
P value		0.001	0.074	0.010	0.353	0.443

Notes: [a] indicates t-value, - indicates that Fisher's exact probability method was used

2.5 Multifactorial Logistic Regression Analysis of Factors Influencing the Severity of RDS in Preterm Infants

A multifactorial logistic regression analysis was performed with no RDS in preterm infants as the reference, mild RDS in preterm infants as the dependent variable （assignment: yes =1, no =0）, and gestational age （assignment: measured value）, birth mass （assignment: measured value）, 1-min Apgar score ≤ 7 （assignment: yes =1, no =0）, 5-min Apgar score ≤ 7 （assignment: yes =1, no =0）, and vitamin A deficiency （assignment: yes =1, no =0） as the independent variables. The results of multifactorial logistic regression analysis with yes =1, no =0 as independent variables showed that gestational age was an influential factor in the development of mild RDS in preterm infants （P<0.05）, as shown in table 5. Taking preterm infants who did not develop RDS as the reference, with no RDS in preterm infants as the reference, the occurrence of severe RDS in preterm infants as the dependent variable（value: yes =1, no =0）, and the gestational age（value: real=0）as the indicator. Gestational age（assigned value: measured value）, birth weight （assigned value: measured value）, 1-min Apgar score （assigned value: measured value）, and birth weight （assigned value: measured value） were used as reference variables. Gestational age （assignment: measured value）, birth weight （assignment: measured value）, and 1-min Apgar score ≤7 （assignment: yes =1, no =0）, 5 min Apgar score ≤ 7 （assignment: Yes = 1, No = 0）, vitamin A deficiency （assignment: Yes = 1, No = 0）, and Vitamin B deficiency （assignment: Yes = 1, No = 0） as independent variables. Logistic regression analysis showed that birth mass and vitamin A deficiency were the most important factors in the development of severe severe respiratory syndrome in preterm infants. The results of multifactorial Logistic regression analysis showed that birth body mass and vitamin A deficiency were the factors influencing the development of severe RDS in preterm infants （P<0.05）, as shown in table 6.

Table 5 Multivariate Logistic regression analysis of influencing factors of mild RDS in preterm infants

Variable	*B*	*SE*	Wald χ^2值	*P* value	*OR*（95%*CI*）
Intercept	8.682	3.202	7.351	0.007	—
Gestational age	-0.251	0.117	4.599	0.032	0.778（0.619, 0.979）
Birth weight	-0.631	0.477	1.750	0.186	0.532（0.209, 1.355）
1 min Apgar score ≤7	0.591	0.419	1.989	0.158	1.806（0.794, 4.110）
5 min Apgar score ≤7	0.504	0.622	0.658	0.417	1.656（0.489, 5.605）
Vitamin A deficiency	0.449	0.366	1.500	0.221	1.567（0.764, 3.213）

Notes: Reference to preterm infants without RDS; - indicates that this data is not available

Table 6 Multivariate Logistic regression analysis of influencing factors of severe RDS in preterm infants

Variable	*B*	*SE*	Wald χ^2值	*P* value	*OR*（95%*CI*）
Intercept	11.244	4.454	6.373	0.012	—
Gestational age	-0.272	0.170	2.549	0.110	0.762（0.546, 1.064）
Birth weight	-2.431	0.834	8.503	0.004	0.088（0.017, 0.451）
1 min Apgar score ≤7	-0.500	0.862	0.336	0.562	0.607（0.112, 3.289）
5 min Apgar score ≤7	1.527	1.044	2.140	0.143	4.604（0.595, 35.616）
Vitamin A deficiency	1.922	0.506	14.448	<0.001	6.835（2.537, 18.416）

Notes: Reference to preterm infants without RDS; - indicates that this data is not available

3 Discussion

The current clinical treatment of RDS in preterm infants is based on ventilator supportive therapy and PS replacement therapy, but the treatment of severe RDS in preterm infants is more difficult and expensive, and there is a greater possibility of sequelae such as bronchopulmonary dysplasia. Since RDS is the main cause of death in preterm infants, it is important to understand the factors influencing the development of RDS in preterm infants and to carry out targeted prevention in order to minimize the occurrence of preterm infants with RDS, especially severe RDS, improve the clinical prognosis of preterm infants, and reduce the morbidity and mortality rate of preterm infants. Studies have shown that the occurrence of RDS in preterm infants is influenced by many factors[9-11], among which low birth mass is a risk factor for the occurrence of RDS in preterm infants of different gestational ages[12]. In the present study, we found that gestational age and body mass were the factors influencing the occurrence of RDS in preterm infants through multifactorial logistic regression analysis, which was consistent with the above findings.

In recent years, studies on the application of vitamins A, D, and E in neonatal diseases have attracted much attention[13-15], among which more studies on the application of vitamin D in neonatal diseases have been reported, but fewer studies have been reported on the relationship between vitamins A and E and RDS in preterm infants. Vitamin A is a fat-soluble vitamin necessary for the growth and development of epithelial cells, and studies have shown that vitamin A deficiency is not only related to the occurrence of many diseases in preterm infants [16], but also plays an important role in the various stages of lung development, such as its role in the retinoic acid receptor of lung tissues and up-regulate the expression of the SP-B gene, which directly promotes the synthesis of PS[17]. The results

of animal experiments show that vitamin A can promote the maturation of fetal lungs in animals, and vitamin A deficiency in the early stages of gestation can lead to poor development of fetal lungs, and vitamin A deficiency in the later stages of gestation can lead to defective alveolar formation[18-19]. Meng Jun et al[20] showed that serum vitamin A levels were significantly lower in the RDS group than in the non-RDS group, but Dai Yuqing et al[21] found no statistically significant differences in serum vitamin A levels among preterm infants of different gestational ages and birth masses. The results of this study showed that the preterm infants in the RDS group had a lower gestational age and body mass than those in the non-RDS group, the proportion of infants with 1-min Apgar score ≤7, the proportion of infants with 5-min Apgar score ≤7 were higher than those in the non-RDS group, and the level of vitamin A in umbilical cord blood was lower than those in the non-RDS group; the results of the multifactorial logistic regression analysis showed that the gestational age, body mass, and vitamin A level in umbilical cord blood were factors influencing the occurrence of RDS in preterm infants. The results of multifactorial logistic regression analysis showed that gestational age, body mass at birth and cord blood vitamin A level were the factors influencing the occurrence of RDS in preterm infants.

In recent years, there has been an increasing number of studies on the relationship between vitamin A and neonatal RDS. ELFARARGY et al[22] showed that serum vitamin A levels in RDS children graded III-IV were significantly lower than those in non-RDS newborns; JIANG Xue[23] showed that serum vitamin A levels in RDS children with a gestational age of 34-36 weeks were lower than those in non-RDS preterm infants, but serum vitamin A levels did not correlate with the severity of RDS; another study showed that serum vitamin A levels did not correlate with the occurrence of neonatal RDS[24-25]. The results of Jiang Xue[23] showed that serum vitamin A levels were lower than those of non-RDS preterm infants at gestational age of 34-36 weeks, but there was no correlation between serum vitamin A levels and the severity of RDS. Another study showed no correlation between serum vitamin A levels and the occurrence of RDS in newborn infants[24-25]. Therefore, in this study, we chose to collect umbilical cord blood from preterm infants at the time of birth to measure vitamin A and E levels, and found that the umbilical cord blood vitamin A levels of preterm infants with severe RDS were lower than those of preterm infants with mild RDS, and the incidence of vitamin A deficiency was higher than that of preterm infants with mild RDS; further, we performed multifactorial logistic regression analysis, and found that vitamin A deficiency was not an influencing factor on the incidence of mild RDS, but rather a factor in the incidence of severe RDS in preterm infants. Further multifactorial logistic regression analysis revealed that vitamin A deficiency was not a factor influencing the occurrence of mild RDS in preterm infants, but a factor influencing the occurrence of severe RDS in preterm infants,

suggesting that vitamin A deficiency had a greater influence on the occurrence of severe RDS in preterm infants.

Vitamin E is also known as tocopherol, and more studies have been conducted on α-tocopherol and γ-tocopherol. The results of animal experiments showed that after maternal supplementation with food containing α- and γ-tocopherols, the lung growth of rat fetuses with pulmonary dysplasia was accelerated, and pulmonary dysplasia and vascular remodeling were improved, suggesting that vitamin E plays an important role in the process of lung development[26]. The results of a randomized controlled trial by RUMBOLD et al[27], which included 1, 877 women, showed that the incidence of neonatal RDS in pregnant women taking vitamins C and E was significantly lower than that in those taking placebo, suggesting that vitamin E may be associated with the occurrence of neonatal RDS. The results of this study showed that the cord blood vitamin E level of preterm infants in the RDS group was lower than that in the non-RDS group, but there was no statistical difference between the cord blood vitamin E level and the rate of vitamin E deficiency in preterm infants with different severity of RDS, and the results of the multifactorial logistic regression analysis showed that the cord blood vitamin E level was not an influencing factor on the occurrence of RDS in preterm infants, which is in line with the results of the previous study[25]. The reasons for this are as follows: （1） cord blood/serum vitamin E levels may be related to gestational age[28], and serum vitamin E levels were significantly lower in preterm infants with RDS at a gestational age of >32 weeks or a birth weight of >1, 500 g[24]; alveolar type II epithelial cells take up vitamin E mainly from HDL during the process of synthesizing PS and alveolar type II epithelial cells express at least three receptors for HDL, the most important of which is the scavenger receptor, which is the most important one. The most important of them is the scavenger receptor class B type I（SR-BI）, and SR-BI expression is increased in vitamin E deficiency to enhance the uptake of vitamin E and increase the concentration of vitamin E in the lung tissue, therefore, cord blood/serum vitamin E levels may not fully reflect the concentration of vitamin E in the lung tissue[29].

It should be noted that vitamins A and E in preterm infants are mainly transported through the maternal placenta, and vitamin A and E deficiency in preterm infants may be a continuation of maternal vitamin A and E deficiency. Jiang Hongqing et al[30] showed that the serum vitamin A level of pregnant women under routine health care was low in late pregnancy, and the incidence of vitamin A deficiency was 35.10%, and the incidence of abnormal serum vitamin E level （mainly vitamin E overdose） was 15.32%. Therefore, supplementation of vitamin A in pregnancy may be beneficial to reduce the incidence of preterm RDS, especially severe RDS, or improve the prognosis of such preterm infants, but it is not a good choice. In addition, although vitamin E is involved in the synthesis of PS, is secreted into the alveolar space, and protects PS lipids from oxidation[4, 29], and maternal vitamin E supplementation

has been shown to improve fetal lung dysplasia and vascular remodeling[26], there are fewer studies and lack of human trials on the relationship between vitamin E and neonatal RDS. However, in view of the fact that there are fewer reports on the relationship between vitamin E and neonatal RDS and the lack of human trials, the relationship between vitamin E and the occurrence and development of RDS in preterm infants still needs to be further investigated.

In conclusion, the occurrence of RDS in preterm infants is related to many factors, and the cord blood vitamin A and E levels of preterm infants with RDS are lower, and the cord blood vitamin A level is a factor influencing the occurrence and severity of RDS in preterm infants, so it is recommended that vitamin A supplementation be provided during pregnancy to minimize the occurrence of preterm infants with RDS and reduce the severity of RDS, but in the present study, we could not detect vitamin A and E levels in preterm mothers due to a smaller sample size. However, the sample size of this study was small, and we were unable to examine the levels of vitamin A and E in preterm mothers, so we are unable to identify the causes of vitamin A and E deficiency in preterm infants, and to guide the supplementation of vitamin A in pregnancy, etc. The relationship between vitamin E and RDS in preterm infants also needs to be investigated in the future by enlarging the sample size, and by combining multicenter research.

Authors' contributions: Liu Weina proposed the research idea and was responsible for designing the research plan and drafting the paper; Liu Weina, Ge Haiyan, and Ma Jing carried out data cleaning and statistical processing, and drawing of graphs and tables; Ge Haiyan and Ma Jing revised the paper; Bai Xingyu and Cui Shifang screened the subjects of the study, and collected and organized the data, and collected the specimens, etc.; Cao Qinying and Qiao Yanxia were responsible for the quality control of the paper, and the revision, supervision and management of the paper as a whole. They were responsible for the overall supervision and management of the article.

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